DETAILED ACTION

Applicant's arguments filed 06/23/2009 have been fully considered but they are not persuasive. The amendment has been entered. Claims 17-8, 18, 20-30, 33, 38-39 are pending. Claims 20-30 are withdrawn. Claims 1-6, 9-17, 19, 31-32, 34-37 are canceled. Claims 7-8, 18, 33, 38-39 are under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim7-8, 18, 33, 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Plotkin et al,** [EP 0389286 B1, Date of publication 26.09.1990 (IDS)]; **Paoletti et al** (US Patent No. 6,267,965 B1) in view of **Endresz et al** [Vaccine, 19: 3972-3980, 2001 (IDS)]; **Mach et al,** [Journal of Virology, 11881-11892, 2000 (IDS)].

Claims 7, 8, 18, 33 are directed a composition comprising a plurality of nucleic acid molecules, wherein the nucleic acid molecules comprise nucleotide sequences encoding different human cytomegalovirus (HCMV) polypeptides that induce a neutralizing antibody response, wherein the HCMV polypeptides comprise: glycoprotein M (gM), or an antigenic fragment of gM, and glycoprotein N (gN), and or an antigenic fragment of gN; wherein the nucleic acid molecules comprise DNA plasmids. Newly added claims limit the composition of claim 7, wherein the composition comprises a plurality of sets of nucleic acid molecules, each

set of nucleic acid molecules encoding at least two different HCMV polypeptides, and each molecule of a set encoding the same HCMV polypeptides and claim 39 limits the composition of claim 7, wherein the HCMV polypeptides further comprise glycoprotein B (gB), or an antigenic fragment thereof.

Plotkin et al teach a composition comprising an adenovirus encoding different human cytomegalovirus (HCMV) subunits for use of the glycoprotein gB subunit of this vaccine, and other subunits of HCMV which may be employed in the production of a vaccine selected from the gA/gB, or gcII [(gM (UL100) and gN (UL73)] as in the instant invention or gcII or immediate early subunits of the human virus (column 4, lines 18-25) **(claims 7-8, 33, 38-39).** Plotkin et al teach a human cytomegalovirus subunit protein produced by an adenovirus expression vector, comprising a human cytomegalovirus (HCMV) vaccine, in that the subunit protein is gcII, and the subunit protein is produced in an adenovirus vector under the control of an expression control sequence, said virus being capable of expressing said subunit in vitro in a host cell or in vivo in a human (column 8 under claims). Plotkin et al teach the recombinant adenovirus containing the gcII, it is in orally administrable unit dose form for use as a vaccine in a pharmaceutical carrier (column 8 under claims) **(claim 18).** Plotkin et al teach the recombinant virus may also contain multiple copies of the HCMV subunit, or alternatively, the recombinant virus may contain more than one HCMV subunit type, so that the virus may express two or more HCMV subunits or immediate-early antigens and subunits together (column 4, lines 50-55) **(claim 33).** Plotkin teaches the inoculation of Ad5/gB (gB a HCMV subunit) immunization in hamsters induced neutralizing antibody to HCMV as detected by the plaque-reduction neutralization assay (column 7, lines 36-50). Plotkin suggests the vaccine is expected to provide analogous results in humans as in the hamster model, i.e. production of neutralizing antibody and also like the HCMV gB subunit of gcII subunit of the HCMV may be expressed in a

recombinant adenovirus with analogous results (column 7 lines 50-55, column 8, lines 1-8). **Paoletti et al** taught expression of various CMV proteins individually and in combination utilizing poxvirus vectors. Plotkin/ Paoletti differ from the present invention for not teaching a single gB plasmid also comprising the gcII (gN and gM) vaccine composition.

However, at the time of the instant invention **Endresz et al,** teach optimization of DNA immunization against human CMV (title). Endresz et al, discusses several approaches have been used to develop an effective and safe subunit HCMV vaccine and recombinant adeno-, vaccinia-, and canarypox-viruses expressing the gB or IE proteins induced antibody and CTL responses specific to the inserted genes in experimental animals, whereas, the canarypox-gB recombinant induced no or only minimal levels of gB-specific antibodies in humans, it did prime the antibody response for a Towne strain-booster (p 3972, 2nd column bridge p 3973, 1st column). Endresz et al, teach that mice injected with plasmids carrying the full length membrane anchored glycoprotein gB of the HCMV or the secreted forms of the glycoprotein gB of the HCMV the secreted form induced higher significantly higher antibody titers than the plasmid carrying the membrane bound form of gB and moreover priming with the plasmid carrying the secreted gB form followed by boosting with the gB protein subunit resulted in high neutralizing antibody response than the membranous gB form (abstract; figure 3; and under results). Endresz et al, suggest for high neutralizing antibody responses by priming with plasmid secretory form gB of HCMV followed by gB protein boost in mice might be suitable in human immunization as compared to parallel viral protocols (p 3977, 2nd column). **Mach et al,** supplement the teachings of Endresz by teaching thus far the gB and gH have been identified as major targets for the neutralizing immune response in human but additional antigens must contribute to the induction of neutralizing antibodies based on preabsorbption studies of human sera with gB or gH (p 11891, 1st column). Mach et al teach glycoprotein gM (UL100) and gN

(UL73) of the gcII form a complex in Cos cells cotransfected with the plasmid gM (UL100) and the plasmid gN (UL73) allowing the transport of the gM-gN complex to the compartments of the secretory pathway (figure 3). Mach et al teach the gM-gN complex reactivity with sera from HCMV-seropositive donors, whereas most sera failed to react with either gM or gN when expressed alone, 62% of sera were positive for the gM-gN complex and because a murine monoclonal antibody reactive with gN in the gM-gN complex efficiently neutralizes infectious virus, the gM-gN complex may represent a major antigenic target of antiviral antibody responses (abstract). As such Mach taken with Endresz provide sufficient motivation for one of ordinary of skill in the art to include in the adenovirus carrying the gB subunit the gcII [(gM(UL100) and gN(UL73)] subunits of Mach for priming with said plasmids and boost with their recombinant protein as taught by Endresz.

Accordingly, in view of the teachings of Plotkin/ Paoletti, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to include in the adenovirus of HCMV gB subunit of Plotkin the gcII subunits gM (UL100) and gN (UL73) of Mach for priming with said plasmids and boost with their recombinant proteins as taught by Endresz for a vaccine in humans for inducing neutralizing antibodies against HCMV with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Plotkin suggests production of neutralizing antibody like the HCMV gB subunit of gcII vaccine is expected to provide analogous results in humans as in the hamster model, and since the plasmid carrying the secreted gB form followed by boosting with the gB protein subunit resulted in high neutralizing antibody response than the membranous gB as taught by Endresz. One of ordinary of skill in the art would have been particularly motivated to use plasmid gM (UL100) and the plasmid gN (UL73) for priming as taught Endresz and since the gM-gN complex is the secreted form as taught by Mach and moreover since the secreted

form is better for priming than the membranous form for the production of neutralizing antibodies against HCMV as taught by Endresz. Moreover, one of ordinary of skill in the art would have been particularly motivated to replace the adenovirus of Plotkin with the plasmid technology of the Endresz/Mach since Endresz teaches priming with plasmid containing the secreted form of the HCMV subunit increases the humoral immune response neutralizing antibody of the IgG2a which is associated with Th1 response (cellular immune response) and Mach suggests that the gM-gN complex may represent a major antigenic target for antiviral antibody responses and a highly immunogenic structure for the humoral immune response during natural infection (p 11882, 1st column, 2nd paragraph).

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

A. Applicants assumed the in the previous office action that the Office meant to reject the claims under 35 U.S.C. § 103, not 35 U.S.C. § 102(b). Given this assumption, applicants traverse the obviousness rejection based on the following comments and the attached declaration of an expert in the field of CMV research, Edward S. Mocarski, Jr., Ph.D. ("the Mocarski Declaration," a copy of which is attached as "Exhibit A"), in which Dr. Mocarski explains that the gB glycoprotein is very different from the gcl! (gM/gN) complex, and that experimental results and suggestions relating to gB cannot be extrapolated to hold true for the gcll complex. The present claims are directed to, inter alia, a composition including a plurality of nucleic acid molecules (e.g., plasmids) comprising nucleotide sequences encoding different human cytomegalovirus (HCMV) polypeptides that induce a neutralizing antibody response. The HCMV polypeptides comprise glycoprotein M (gM), or an antigenic fragment of gM, and glycoprotein N (gN), or an antigenic fragment of gN.

For the clarity of the record due to a typographical error the rejection of the claims was based under 35 U.S.C. § 103(a), and not 35 U.S.C. § 102(b). Therefore, the arguments of Mocarski that the gB subunit is distinct from the gcII subunit are persuasive.

B. Applicants argue that Plotkin discloses administering a recombinant adenovirus having a gene encoding the HCMV glycoprotein B (gB) to hamsters, which produced neutralizing antibody to HCMV (see, e.g., Example 3). Although Plotkin suggests in passing (see, e.g., column 8, lines 3-7) that its recombinant adenovirus expression system could be used to express other HCMV subunit proteins, e.g., gcII, the reference does not contain any actual examples of an adenovirus that expresses gcII (i.e., the gM/gN complex), or any example of such an adenovirus being administered to any subject. In fact, when Plotkin filed his priority application in 1989 little was known about exactly what glycoproteins was part of the so-called gcII complex. Endresz describes administering a plasmid encoding gB to mice. There is nothing in this reference about gN and gM. Mach suggests (see, e.g., Abstract) that gM and gN form a complex, and that the gM/gN complex may be an antigenic target of antiviral antibody responses. However, while Mach discloses that the gM-gN protein complex "may represent a major antigenic target of antiviral antibody responses," Mach fails to suggest that gM and gN could be used as a nucleic acid-based vaccine as presently claimed, in addition, Mach ends his paper by stating that "[f]uture experiments will be directed towards defining the functional and immunological properties of the gM-gN complex" (page 11891, left col.). Moreover, the gM- and gN-expressing plasmids disclosed in Mach were used solely to express these polypeptides in vitro. In essence, none of these references discloses any data demonstrating or suggesting that gcII (i.e., gM and gN) could be successfully used as a nucleic acid-based vaccine to induce a neutralizing antibody response against CMV. Nevertheless, the Office Action asserts (at pages

6 and 7) that those skilled in the art would have reasonably expected that plasmids expressing gN and gM could be used as a DNA vaccine, apparently based on the gB data disclosed in Plotkin.

These arguments are not persuasive because the claimed invention is directed to inclusion of well known cytomegalovirus subunits in a plasmid composition.

Plotkin disclosed the gB subunit in an adenovirus vector (see the claims). In addition, Paoletti et al taught expression of various CMV proteins individually and in combination utilizing poxvirus vectors. Mach disclosed the gM- and gN-expressing plasmids. This only differs since they did not include all the well known cytomegalovirus subunits such as gB and gM and gN in a single plasmid. Paoletti et al taught expression of various CMV proteins individually and in combination utilizing poxvirus vectors. They taught expression of well known HCMV subunits either alone or in combinations (see the claims).

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art. See, Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). Here, the prior art taught isolation of plasmid gB, gM and gN and the induction of neutralizing antibodies, as taught by Plotkin.

Thus, one of ordinary skilled in the art at the time of filing would have been amply motivated to include all these HCMV subunits taught by Plotikin/Paletti and Mach that are well known to those skilled in the art, to form a plasmid composition to induce immune response against cytomegalovirus infection. Applicants would have been motivated to form the combined plasmid since Plotikin/Paletti taught the gB subunit is involved in the induction of neutralizing antibody in hamsters and since Mach teaches the gM-gN complex may represent a major antigenic target of antiviral antibody responses.

Here, none of the HCMV plasmid subunits were discovered by the Applicants, and all of the HCMV plasmid subunits were known and taught prior to now claim priority as disclosed by the above cited art. All Applicants have done is include the HCMV subunits well known in a palmed together. Applicants are reminded that the skill level is rather high in this art.

The court in In re O'Farrell stated: "obviousness does not require absolute predictability of success… all that is required is a reasonable expectation of success. See In re O'Farrell, 853 F.2d 894, 895-899 (Fed. Cir. 1988). This is the case now, the differences between what's taught in the prior art and claimed invention is rather obvious. Given the level of skill in this art, fusing well known proteins are notoriously obvious. Applicants at the time of filing in view of above cited art had reasonable expectation of success, because obvious to try the gB and gM or gN as taught by Plotkin so that the virus may express two HCMV subunits together in order to boost the secretion of neutralizing antibodies as taught by Mach render predictable results. In addition, Plotkin suggests production of neutralizing antibody like the HCMV gB subunit of gcII (gM and gN) vaccine is expected to provide analogous results in humans as in the hamster model, and since the plasmid carrying the secreted gB resulted in high neutralizing antibody response than the membranous gB as taught by Endresz. . Hence, the invention as a whole is deemed prima facie obvious absent any unexpected results.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305. The examiner can normally be reached on Monday through Friday from 9 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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